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Review

Sodium Nitroprusside: The Forgotten Vasodilator? A Brief Guide for Informed and Safe Use from Heart Failure to Hypertensive Crisis and Aortic Dissection

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Abstract: Sodium nitroprusside (SNP) is a powerful vasodilator approved for treating acute hypertensive crises, acute heart failure, aortic dissection, and both controlled perioperative hypotension and perioperative hypertension. Its unique ability to cause both venous and arterial dilation makes it an invaluable option in critical care settings. Despite concerns regarding its manageability due to potential toxicity, it is a safe choice if properly used, as highlighted by its short half-life and minimal side effects. This review aims to summarize its pharmacological properties, toxicology, and various clinical applications, particularly focusing on acute heart failure and hypertensive emergencies.

Keywords: sodium nitroprusside; vasodilator; heart failure; acute heart failure; hypertension; heart transplant; pulmonary hypertension; reversibility test

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1. Introduction

Sodium nitroprusside (SNP) is a vasodilator with the ability to cause both venous and arterial dilation. Its use is largely overlooked because of the wrong assumption of its limited manageability. However, if used in the right patient, in the right context, and with the basic notion of pharmacokinetics (important to administer in photo-darkening kits), pharmacodynamics, and toxicology, it turns out to be a substantially safe and extremely manageable drug because of its short half-life (about 2 min). Virtually, there are few/no side effects at therapeutic dosages. From the hemodynamic point of view, SNP exerts effects that are extremely useful for the treatment of numerous patients: reduction in peripheral and pulmonary resistance, increase in cardiac output (CO), and improvement in cardiovascular performance. In this brief review, we will address the most frequent pathologies in which its use could be of utility.

2. Materials and Methods

We have performed a non-systematic review of the literature by applying the search strategy in several electronic databases (MEDLINE, EMBASE, Cochrane Register of Controlled Trials, and Web of Science). We have selected original articles, meta-analyses, and

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review reports in peer-reviewed journals up to September 2024 regarding SNP and its use in clinical practice.

3. Sodium Nitroprusside: Pharmacology and Toxicology

The discovery of SNP occurred in 1849 by Lyon Playfair (1818–1858; English scientist, chemist, and politician, professor of chemistry at the University of Edinburgh). It received its first medical approval for the treatment of severe hypertension by the FDA in 1974 [1]. Actually, SNP is indicated for (1) a prompt reduction of blood pressure of adult and pediatric patients in hypertensive crises; (2) providing controlled hypotension during surgery to reduce bleeding entity; (3) treatment of acute congestive heart failure (HF) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207426Orig1s000lbl.pdf accessed on 29 October 2024). SNP off-label use may include (1) hypertension in the setting of acute ischemic stroke; (2) afterload reduction in acute mitral regurgitation; (3) increase CO in cardiogenic shock and high systemic vascular resistance; (4) acute preload reduction in select patients with valvular aortic stenosis [1,2].

SNP is a water-soluble salt composed of ferrous iron bound with nitric oxide (NO) and five cyanide anions [2]. It is a prodrug that reacts with sulfhydryl groups on erythrocytes, albumin, and other compounds in order to release NO, which is the pharmacologically active principle. Its mechanism of action can be explained by the activation of intracellular guanylate cyclase in vascular smooth muscle cells, forming cyclic guanosine monophosphate (cGMP), avoiding calcium entrance into smooth muscle cells and favoring calcium uptake by the endoplasmic reticulum, which results in vasodilation [3] as described in Figure 1.

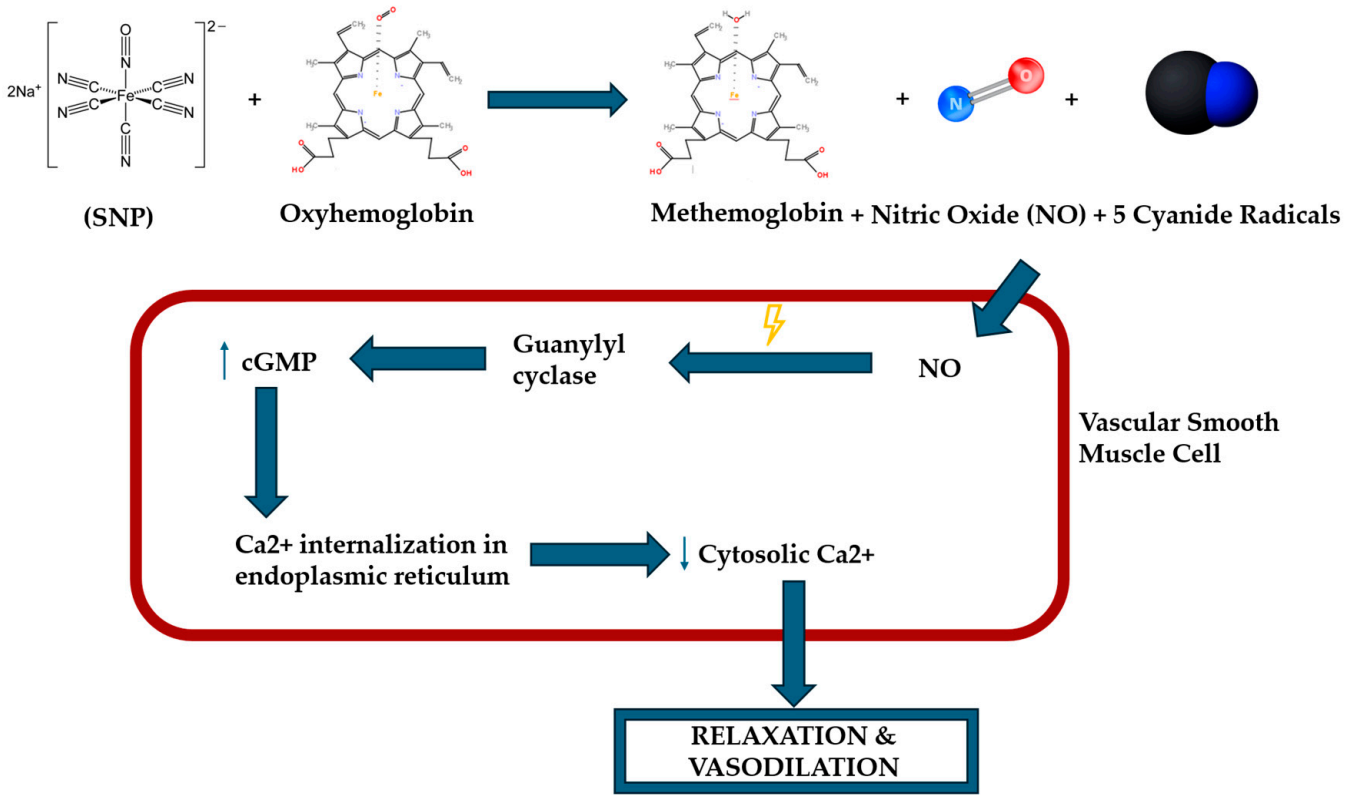

Figure 1. Molecular mechanism of SNP.

Unlike organic nitroderivatives, SNP does not require activation by sulfhydryl group donors to release NO.

SNP determines both arterial and venous dilation [2]. It has been observed that it can also reduce platelet aggregation [2].

In the current practice, SNP administration has been limited by the fear of its toxicity. As stated above, the drug is safe when used at an appropriate dosage according to the therapeutic indications.

It is known that SNP reacts with oxyhemoglobin, forming methemoglobin and releasing NO and five cyanide radicals as shown in Figure 1. The formers are responsible for SNP toxicity [3].

Of these five cyanide ions, it is known that one binds to methemoglobin and produces cyanohemoglobin; three are rapidly metabolized to the less toxic thiocyanate (via the enzyme hepatic rhodanese), which is distributed in the extracellular fluid and slowly eliminated by the kidneys; one forms cyanocobalamin by combining with vitamin B12.

Cyanomethemoglobin can bind to tissue cytochrome oxidase, interfering with oxidative phosphorylation and determining anaerobic metabolism and lactic acidosis [2]. For this reason, lactate evaluation is an excellent surrogate because of the long turnaround time of cyanide concentration measuring. Thus, lactate concentrations or the arterial base deficit can be used to support the diagnosis of cyanide toxicity [3]. However, in patients with HF in whom lactates are a microparameter of "cellular well-being", measurement of metabolites (such as thiocyanates levels) turns out to be important.

The remaining cyanide anions are transported to the liver, where the rhodanase enzyme (thiosulfate sulfurtransferase), using thiosulfate ions, transforms cyanide radicals into thiocyanates, which are excreted in urine. Indeed, infusion rates higher than 2 ug/kg/min can cause cyanide toxicity for sulfur donors and methemoglobin depletion [2]. This enzyme is mainly expressed in liver and blood cells, while other tissues like the brain and heart are exposed to a higher risk of toxicity through the production of reactive oxygen species and cell apoptosis [2].

In summary, SNP causes toxicity by two primary mechanisms: (1) thiocyanate toxicity, which occurs rarely, resulting in tinnitus, mental status alteration, nausea, and abdominal pain; (2) in rare cases, cyanide toxicity may occur, resulting in coma, metabolic acidosis, or respiratory arrest. Prolonged infusions or high infusion rates require close attention to the acid–base balance and mixed venous oxygen concentration, as unexplained acidemia and/or hypoxemia are often early signs of cyanide toxicity [1]. In very rare cases, and in sensitive patients, methemoglobinemia may occur, which may cause symptomatic cellular hypoxia if levels reach more than 15%.

Usually, SNP toxicity is related to a prolonged administration or because of the concomitant presence of renal or hepatic impairment.

Cyanide poisoning can be treated by infusion of both sodium thiosulfate (which is a sulfur ion donor) and hydroxocobalamin with no significant adverse effects. Hydroxocobalamin reacts with cyanide anions, forming cyanocobalamin, which can be eliminated in the urine [3]. Metabolic acidosis treatment is based on sodium bicarbonate administration and 3% sodium nitrite [3]. Sodium nitrite transforms hemoglobin into methemoglobin, which reacts with cyanide anions, reducing their binding with cytochrome oxidase [3]. Finally, an experimental antidote, known as sulfanegen, might be of help in managing cyanide toxicity [4]. It is a prodrug of 3-mercaptopyruvate, orally administrated, that has been reported to reduce oxidative stress in vivo [5]. It can also prevent cyanide poisoning by prophylactic administration 1 h before SNP use. Sulfanegen metabolites convert cyanide anions into thiocyanates [2]. A summary of toxicity and antidotes is reported in Table 1.

Table 1. Summary of toxicity and antidotes.

Sign of Cyanide Toxicity		General Treatment
Central nervous system	Mental status change Seizure Coma	STOP infusion SNP 100% Oxygen infusion (despite normal O_2 saturation) Correction metabolic acidosis with HCO_3
Cardiovascular instability	Hypertension ECG change (arrhythmia, ST depression)	3% sodium nitrite 4/6 mg/kg IV slowly Sodium thiosulfate 150/200 mg/kg IV over 15 min (most utilized over for toxicity prophylaxis)
Increasing metabolic acidosis	Increasing base deficit Lactate augmented	Consider Hydroxocobalamin (Vit B12) 25 mg/h

4. Sodium Nitroprusside and Other Vasodilators: Hemodynamic Effect

SNP is a short-acting intravenous vasodilator that releases NO throughout the circulation, powerfully dilating both arterial and venous vessels. It induces potent pulmonary vasodilation and a direct inhibition of hypoxic pulmonary vasoconstriction [3]. Additionally, it exerts direct effects on the myocardium, lowering the end-diastolic pressure–volume relationship of the left ventricle (LV) [6]. Its great advantage is the immediate onset and the short half-life, dissipating in 1–2 min. SNP is particularly advantageous in acute settings due to its short half-life, rapid action, absence of significant side effects at therapeutic dosage, and lack of tolerance with continuous infusion. However, caution is necessary in patients with significant underlying coronary artery disease not undergoing revascularization, as arteriolar vasodilation may potentially increase myocardial ischemia by causing an intracoronary steal of blood flow away from ischemic areas [2]. A randomized, double-blind, placebo-controlled trial on patients presenting with acute myocardial infarction and high LV filling pressures demonstrated that precocious (<9 h) administration of SNP had a deleterious effect with a higher mortality rate compared to placebo, whereas SNP yielded a beneficial effect if begun later [7]. However, a net benefit in acute infarction occurs when acute mitral regurgitation has set in.

Organic nitrates, including nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate, act as both arterial and venous vasodilators, exerting their effects primarily on larger vessels while having a lesser impact on arterioles, particularly at lower doses. Their effect predominantly targets veins, consequently reducing cardiac preload. On the other hand, arteriolar relaxation reduces systemic vascular resistance, thereby decreasing cardiac afterload. Additionally, they preferentially dilate coronary arteries and arterioles with diameters greater than 100 micrometers, increasing coronary blood flow [8]. The combination of these effects leads to a reduction in myocardial oxygen consumption, providing relief from angina. The major limitation to the prolonged use of organic nitrates is the drug tolerance that might be rapidly developed without an intermittent dose interruption regimen. However, other studies show that increased coronary perfusion pressure via coronary vasodilation may result in a protective effect on the already compromised myocytes [9]; in a randomized selected patient, early infusion of SNP during acute infarction limits complications, possibly by reducing infarct size. It has been reported that the drug is particularly effective in anterior-wall infarction [10]. It is likely that SNP improves CO without increasing myocardial oxygen demand.

Hydralazine is a vasodilator with an unclear mechanism of action. It predominantly exerts its effects at the arteriolar level, with minimal effect on the venous side of the vascular tree [11]. The effects are to relax arteriolar smooth muscle and lower blood pressure. The reduction of vascular resistance may lead to increased heart rate, stroke volume, and CO [11]. Nitrates are NO donors, while hydralazine acts as an antioxidant through the reduction of NO consumption [12]. In the study from Packer et al., an increase

in hemodynamic and ischemic complications (up to 23% of the study subjects) when using hydralazine alone compared with SNP was reported [13]. Hydralazine–nitrate combination therapy may result in a degree of arterial and venous dilation that is similar to that of SNP [14]. However, hydralazine should be administered three times a day, thus reducing compliance. Isosorbide dinitrate is dosed similarly.

The benefit of increased NO in both acute and chronic models of HF is an important pathophysiologic finding. SNP has the advantage of a direct dose/response ratio in terms of clinical benefits that other NO drugs do not have. This is the reason why it is appropriate for the acute setting, while the conventional NO donors have indications mainly in the chronic setting [14].

In the article from Leier et al. evaluating mainly the hemodynamic properties, the different responses after administration of SNP, nitroglycerin, and isosorbide dinitrate were compared by cardiac catheterization; it was demonstrated, in vitro, that SNP causes a greater increase in stroke volume and cardiac index [15]. All three drugs in that study reduced systemic resistance, but the result with SNP was greater, as it was for lung vascular resistance. In addition, unlike nitroglycerin and isosorbide, SNP reduces renal vascular resistance with a marked change in renal hemodynamic performance [15]. SNP combines both arterial and venous dilating properties. This venodilation promotes the shifting of blood volume from the stressed central cardiopulmonary circulation to the unstressed visceral circulation, thereby reducing cardiac preload and central venous pressure [16]. Arterial dilation with reduced afterload facilitates left ventricular emptying, reduces mitral regurgitation, and increases stroke volume [17].

Effective arterial elastance (Ea) expresses the afterload of the LV. It is defined by the ratio of the left ventricular end-systolic pressure (LVESP) to the stroke volume. The LVESP can be approximated to about 90% of the systolic arterial pressure. The left ventricular end-systolic elastance (Ees) is a measure of the myocardium's intrinsic contractility and represents the inotropic efficiency of the LV. Ventricular arterial coupling (VAC:Ea/Ees) expresses the concept that the heart and the arterial system are anatomically and functionally connected structures; thus, VAC refers to the heart's pumping action when connected to the load imposed by the arterial system [18]. The total mechanical energy generated during systole for a given contractility and loading condition is expressed by the sum of stroke work (SW) and the potential energy (PE). SW represents the useful fraction of ventricular energy delivered to the arterial system to ensure an adequate stroke volume; on the other hand, PE represents the ventricular energy dissipated as heat during isovolumetric relaxation [18]. VAC is achieved when the Ea/Ees ratio tends towards unity: under this circumstance, maximum SW is produced. Patients with poor myocardial contractility, expressed by low Ees, exhibit low CO. When systemic tissue perfusion decreases, the renin–angiotensin–aldosterone system and the sympathetic nervous system are hyperactivated to increase intravascular volume and arterial load and prevent systemic hypoperfusion [19], resulting in increased afterload.

Vasodilator therapy, by reducing arterial elastance (Ea), restores ventricular–arterial coupling, leading to increased stroke volume with minimal impact on mean arterial pressure [20]. Hence, the beneficial hemodynamic effects of vasodilator therapy are expected in patients with ventricular–arterial uncoupling, characterized by low CO, poor LV systolic function, and increased arterial elastance (Ea). It has been highlighted that, in advanced HF patients undergoing right heart catheterization, SNP infusion significantly increased the cardiac index ($2.1 +/- 0.5$ vs. $2.6 +/- 0.5$ L/min/m^2, $p < 0.004$), reduced pulmonary artery wedge pressure ($25 +/- 6$ vs. $14 +/- 4$ mmHg, $p < 0.0001$), and decreased the severity of mitral regurgitation [21]. Also, in a meta-analysis comparing inotropes, SNP produces a similar increase in CO but a greater reduction in PCWP [22]. In patients with dilated

left ventricles and mitral regurgitation, low afterload promotes improved CO and organ perfusion [23]. SNP rapidly and markedly improves cardiac function in decompensated HF patients where severe left ventricular systolic dysfunction and severe aortic stenosis are recognized as major causes. It represents a safe and effective bridge to aortic-valve replacement or oral vasodilator therapy in these critically ill patients [24].

Conversely, in patients with preserved VAC, such as those affected by HF with preserved ejection fraction (HFpEF), the use of SNP may increase the risk of a drop in left ventricular stroke volume and blood pressure because of a sharp reduction in preload and afterload [25]. This type of patient has a reduced preload reserve and does not tolerate venodilation well. As recently described in a review study, in the evaluation of left ventricular pressure–volume curves, the use of SNP gives an advantage to patients with high filling pressures, severe LV dilation, and afterload-dependency [26]. Then, when ventricular function is normal or minimally or moderately impaired, stroke output usually remains unaltered while LVEDP falls. This happens because the preload reduction occurs at the same extent as the impedance to ejection [27]. The ideal acute HF (AHF) patient for vasodilator treatment has low stroke volume, low CO, high left-sided filling pressures, a relatively preserved right ventricle, and normal or elevated systemic vascular resistance. A Schematic view of SNP use is reported in Figure 2.

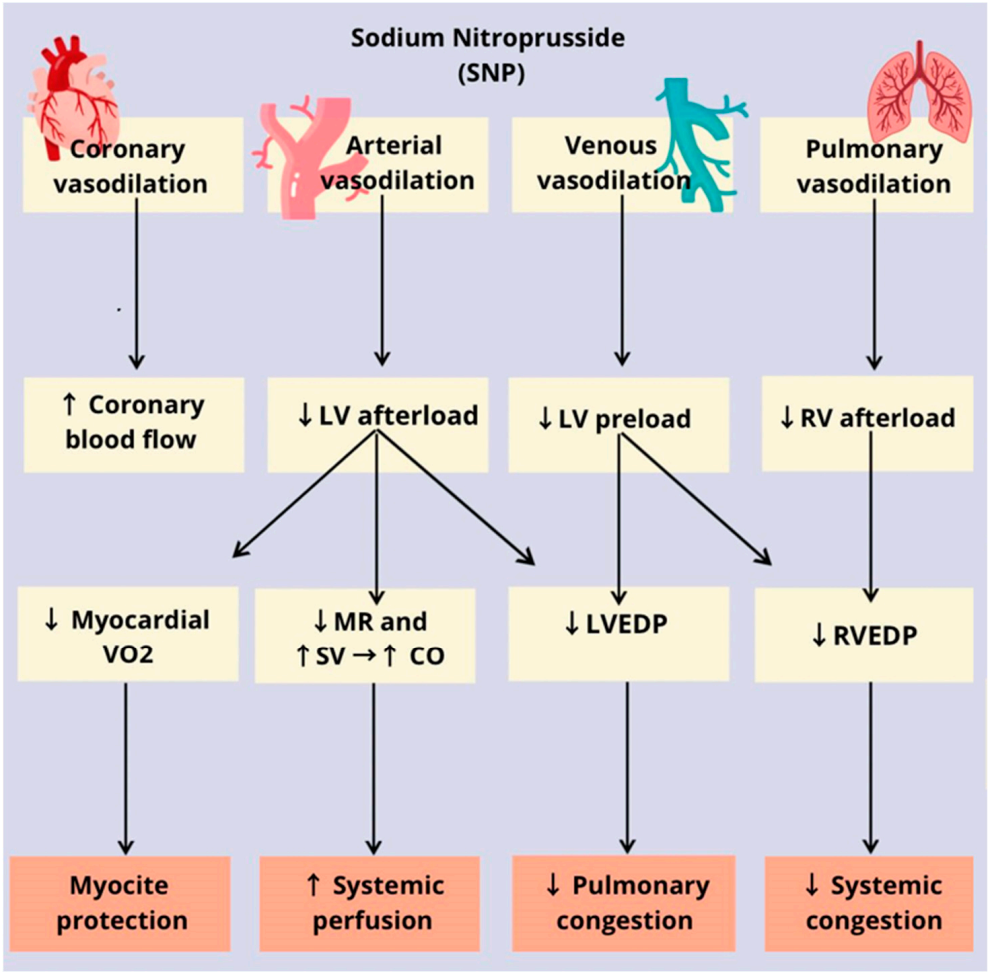

Figure 2. Schematic view of the effect of SNP on different vascular districts.

5. Sodium Nitroprusside in Acute Heart Failure and Heart Transplant

The term acute AHF refers to the sudden or progressive development of HF symptoms and/or signs severe enough to prompt the patient to seek immediate medical care, resulting

in an unplanned hospital admission or a visit to the emergency department [28]. Each episode is associated with high mortality and an increase in re-hospitalization rates [29]. A diagnosis of AHF is made when a decompensation of pre-existing cardiomyopathy occurs.

Older guidelines by the European Society of Cardiology [30] classified patients into six groups (I–VI) based on clinical and hemodynamic characteristics: (I) acute decompensated HF (ADHF), (II) hypertensive AHF, and (III) AHF with pulmonary edema, accounting more than 90% of presentations to hospital. ADHF patients typically show mild–moderate symptoms, whereas those patients with AHF and pulmonary edema (III) have a clinical presentation mainly with respiratory distress and hypoxemia and display a continuum of severity from low-output states (IVa) to outright cardiogenic shock (IVb). High-output failure (V) remains an uncommon cause of AHF and is usually associated with anemia, thyrotoxicosis, and Paget's disease. The main clinical characteristics are warm extremities and pulmonary congestion, and, in the case of systemic sepsis, it results in hypotension. This classification also includes the right-sided HF category (VI), predominated by patients with pre-existing lung disease and cor pulmonale, although acute myocardial ischemia/infarction affecting the right ventricle is also included in this group.

The pathophysiology of AHF is associated with increased ventricular filling pressures and/or decreased cardiac systolic output, leading to clinical manifestations of congestion and hypoperfusion [31].

The more recent ESC guidelines describe four major clinical presentations with possible overlaps between them: ADHF, acute pulmonary edema, isolated right ventricular failure, and cardiogenic shock [28].

In light of this classification, it is necessary to re-optimize or change the medical therapy, including intravenous treatment, in order to enhance the patient's hemodynamics through the reduction of congestion, typically achieved, in most cases, with diuretics and by improving cardiac contractility using inotropes where there is evidence of reduced CO leading to hypoperfusion.

In the case of acute cardiogenic pulmonary edema, which is one of the clinical manifestations of AHF due to valvular heart disease or by an increased afterload and/or predominant LV diastolic dysfunction, a key role is played by vasodilators like SNP in combination with diuretics. In this clinical scenario, pulmonary edema is caused by fluid redistribution to the lungs rather than fluid accumulation. It is suggested that this mechanism is due to an increase in vascular stiffness at the venous level, resulting in a decrease in vascular capacity with an increase in venous return and thus preload, as well as at the arterial level with an increase in afterload, leading to increased intracardiac pressures transmitted back to the pulmonary veins and lungs [32].

The role of vascular mechanisms is relatively more pronounced in cardiovascular HF compared to decompensated HF [33], in which fluid retention is a key factor.

These considerations about their pharmacodynamics are necessary to understand why vasodilators are important for the relief of symptoms, in place of diuretics, in patients where acute pulmonary edema is triggered by increased afterload and the redistribution of fluid to the lungs, with or without minimal fluid accumulation.

In this regard, SNP is an excellent vasodilator, equally potent on both arterial and venous vessels [34], unlike nitrates, which mainly act on the venous side [35].

This vasodilatation leads to decreased venous return by increasing venous capacity (reduced preload), as well as to a reduction in resistance (lowered afterload) and splanchnic vasodilation [36], eventually resulting in the redistribution of the blood volume from the central (pulmonary) to the systemic vasculature, providing symptom relief (Figure 1) [37].

SNP enhances renal blood flow and lowers renal vascular resistance, ultimately promoting increased diuresis. This additional effect further aids the preload reduction [15].

The use of vasodilation obtained with SNP in AHF was introduced with the study conducted by Cohn and Burke entitled "Nitroprusside", published in the Annals of Internal Medicine in 1979, which discusses the pharmacological properties and clinical uses of SNP, particularly in the context of HF and acute myocardial infarction. The authors explore its vasodilator effects, emphasizing how SNP effectively lowers both preload and afterload, leading to improved hemodynamics in patients with decompensated HF [38].

According to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF, in case of acute pulmonary edema, first oxygen and diuretics should be administered; then, i.v. vasodilators, nitrates, or SNP may be given if systolic BP (SBP) is >110 mmHg (Class IIB, level B). This evaluation has been performed in two Italian high-volume centers for advanced and acute HF, in accordance with their experience, describing the benefit in terms of significant reduction of NT pro-BNP biomarker even in patients where treatment was started with BP less than 110 mmHg [39]. The NT pro-BNP reduction was independent of the initial SBP values, suggesting a generalized beneficial effect of SNP in the setting of AHF. Also, in the 2016 guidelines, the blood pressure threshold was <90 mmHg and this value was arbitrarily decided.

The level of recommendation is low and does not exceed the indication of diuretics (Class I, level C) because two recent randomized trials that compared standard care with early, intensive, and sustained vasodilation (The GALACTIC and the Elisabeth Randomized Clinical Trials) did not demonstrate a favorable effect of intravenous vasodilators compared to high-dose diuretics [40,41]. However, ELISABETH and GALACTIC trials focused on the very early use (in the first hours from AHF diagnosis) of high doses of venous vasodilators rather than on a prolonged and carefully titrated strategy of mixed arterial and venous vasodilation [39].

The ESC recommends a more proactive approach in the use of vasodilators, advising the early administration of SNP and isosorbide dinitrate, particularly in patients with elevated resistance and hypertension, unlike the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines, which are more cautious and reserved in their use.

In clinical practice, in this setting, SNP is administered intravenously as a continuous infusion. It has a rapid onset of action. In patients with decompensated HF, the initial dosage ranges from 0.3 to 0.5 μg/kg/min. This dose can be doubled every five minutes, with a maximum limit set at 2 μg/kg/min. The objective is to lower ventricular filling pressures to nearly normal levels. Hemodynamic targets are traditionally defined as pulmonary artery wedge pressures below 15/16 mmHg and right atrial pressure under 8 mmHg. The infusion of SNP should be stopped if sustained arrhythmias occur if systolic blood pressure falls below 80 mmHg, or if there is symptomatic hypotension, deterioration in clinical status, a heart rate below 50 beats per minute, or a rapid heart rate decrease of more than 20% [37].

Although there is some hemodynamic evidence indicating the potential benefits of nitrate treatment for AHF, significant gaps remain in the availability of robust data from well-controlled prospective studies focused on patient outcomes and symptom relief. Additionally, there are no clear guidelines for physicians on how to adjust dosages or monitor blood pressure effectively.

Existing trials about this strategy have been more often small and insufficiently powered [42].

Pulmonary Hypertension and Heart Transplant

Pulmonary hypertension (PH) is characterized by persistently increased pressure in the pulmonary arteries. The PH task force has defined new criteria for the different hemo-

dynamic types of PH that occur with left heart disease based on (1) isolated postcapillary PH characterized by pulmonary artery wedge pressure > 15 mmHg and mean pulmonary arterial pressure (mPAP) > 20 mmHg and pulmonary vascular resistance (PVR) < 2 Woods units (WU); (2) combined post- and precapillary PH (cpCPH) where pulmonary artery wedge pressure > 15 mmHg, mPAP > 20 mmHg, and PVR $\geq$ 2 WU. Secondary PH is initially reversible, but, because of the remodeling process of the pulmonary vascular system, it may become fixed. Limitations in defining both the time for and amount of reversibility lack clarity.

Clinical classification of pulmonary hypertension.

GROUP 1 Pulmonary arterial hypertension (PAH).

GROUP 2 PH associated with left heart disease.

GROUP 3 PH associated with pulmonary disease and/or hypoxemia

GROUP 4 PH associated with pulmonary artery obstruction.

GROUP 5 PH with unclear and/or multifactorial mechanisms

In the Group 2 PH evaluation of heart transplants, hemodynamic alterations such as increased mean pulmonary pressure, transpulmonary gradient, and PVR are associated with a poor prognosis.

A PH reversibility test is indicated in patients with advanced HF who are candidates for a heart transplant if they have a systolic PAP > 50 mmHg and PVR > 3 WU. For this purpose, SNP is often the drug of choice, although other agents can be used with progressive titration while maintaining a systemic systolic pressure > 85 mmHg [43,44].

Moreover, even in patients who are not candidates for transplantation, a reduction in PSR and PH following SNP infusion is associated with a more favorable prognosis in patients with advanced HF and combined PH [45].

The article from Pasero et al. shows a reduction in PVR and mPAP following the administration of either inhaled NO (iNO) or SNP. A better effect of NaNTP has been attributed to a left ventricle post-load reduction. However, iNO has two important advantages: the absence of systemic hypotension and the selectivity for the pulmonary vascular system, as underscored by TPG reduction [46]

In the Group 1 PH acute pulmonary vasoreactivity testing aims to identify responsive patients who might benefit from treatment with high-dose calcium channel blockers (CCBs) and is recommended only in patients with PAH that is idiopathic, toxic, and hereditary.

The agents recommended for testing are NO and iloprost, both by inhalation and iloprost or, alternatively, there is as much data to support the use of intravenous (i.v.) epoprostenol, but, because of the need for incremental doses and repeated measurements, the test takes much longer and is, therefore, less feasible [47].

However, other data comparing SNP with iNO, which is a selective pulmonary vasodilator in patients affected by chronic pulmonary hypertension, show improved cardiac performance without altering RV contractility. SNP caused a similar degree of pulmonary vasodilation but, in contrast with iNO, it caused systemic hypotension associated with an increase in RV contractility [48].

Experimental animal models of blood-perfused isolated rat lungs have shown that iNO and SNP dilate small-resistance arteries and veins, whereas SNP, but not iNO, dilates larger capacitance arteries and veins [49].

6. Sodium Nitroprusside in Emergency Hypertension and Aortic Dissection

6.1. Hypertensive Emergency

SNP represents a cornerstone in the treatment of hypertensive emergencies because it possesses many characteristics that make it the ideal drug for the treatment of these

conditions. Its rapid onset, easy titration, the prompt dissipation of its effects after discontinuation, and its nearly universal efficacy (regardless of the etiology of hypertension) contribute to the drug's popularity [3,50]. The drug acts by reducing both arterial and venous resistances through the production of cyclic GMP and sequestration of intracellular calcium. This mechanism results in decreased peripheral resistances without causing increased venous return; thus, SNP is particularly useful for treating patients with hypertensive crisis and acute pulmonary edema [51]. In addition, because of its rapid onset, it is used to control blood pressure intraoperatively or in the immediate postoperative period. In these patients, adequate pressure control is important to reduce the risk of bleeding from suture sites, myocardial infarction, or stroke [52].

Therapy should be started by intravenous infusion at an initial rate of 0.3 micrograms per kilogram/minute up to a maximum rate of 10 micrograms per kilogram. Intensive hemodynamic monitoring is desirable when administering SNP in this setting, and possibly continuous blood pressure monitoring using a permanent arterial line is required [1].

6.2. Aortic Dissection

Hypertension is considered the main risk factor for aortic dissection (AD) [53]. The role of hypertension is related both to increased wall tension and to the action of pro-inflammatory triggering through the recruitment and activation of macrophages. These mechanisms lead to increased stiffness of the aortic wall, predisposing to the formation of dissections or aneurysms [54].

The term AD describes a tear in the tunica intima of the aorta that extends into the media of the wall. Blood can enter through this tear, leading to the formation of a false lumen bounded by the inner and outer layers of the media, which can result in reduced systemic blood flow.

In the case of AD, strict control of blood pressure with a reduction of the rate of pressure rise during systole, as well as heart rate decrease, is essential to prevent further propagation of the dissection. The shear force within the aorta is defined by the change in pressure over time (dP/dT), thus highlighting that simply lowering the blood pressure is not sufficient. It is expected that, following the addition of a vasodilator to lower blood pressure, an increase in heart rate and, thus, in dP/dt occur [55].

Hence, the vasodilator has to be combined with a beta-blocker such as labetalol to achieve both a reduction in blood pressure and heart rate, resulting in dP/dt decrease [38].

The treatment of choice for all ascending AD is medical therapy along with emergency surgery unless there is a contraindication to surgery, while medical treatment is preferred for descending aortic dissections [53,56].

The goal of SNP therapy is to reduce systolic blood pressure below 120 mmHg or to the lowest possible pressure value to ensure adequate perfusion to the peripheral vascular beds [51]. SNP is administered by titrated infusion at the dose of 0.5–1.5 μg/kg/min [55]. In addition, AD-related pain may result in increased blood pressure and heart rate; thus, treating pain with intravenous opioids may be helpful in controlling blood pressure and heart rate, too [50,51].

7. Sodium Nitroprusside in Pediatric Setting

SNP is also approved for pediatric use, similar to its use in adults, as indicated by the FDA (https://www.fda.gov/media/103569/download accessed on 1 December 2024). It is a potent antihypertensive agent that is also recommended for the treatment of hypertensive emergencies in pediatric patients [57]. Severe hypertension in this setting occurs in the course of many cases of nephropathy or following surgery and contributes greatly to mortality and morbidity. An old study performed on 20 children with hypertensive crisis

demonstrated the efficacy of the drug prepared by dissolving 35 mg in 500 mL of a solution with dextrose at 5% [58]. The desired blood pressure level was achieved in all patients with a diastolic pressure between 70 and 90 mmHg and without any changes in heart and respiratory rate. Moreover, SNP is an excellent drug for the control of hypertensive crisis in pediatric patients, both in terms of the potency of the hypotensive effect and in terms of the time required to reach optimal blood pressure values [58].

SNP may be safely and effectively used in the management of circulatory disorders in neonates, as reported in a pilot study enrolling 58 neonates, all refractory to conventional intensive therapy [59]. Specifically, 11 neonates with severe respiratory distress syndrome, 15 with persistent PH of the newborn, 28 with clinical shock, three with systemic hypertension, and two with pulmonary hypoplasia were treated with SNP, infused at 0.2 to 6.0 μg/kg/min for periods of from 10 min to 126 h. Infants with severe respiratory distress syndrome had a high survival rate (up to 82%), showing increased PAo_2 and decreased $Paco_2$ or peak inspiratory pressure. A variable response was observed in infants with persistent PH, while those presenting shock had improved perfusion, urine output, and serum bicarbonate levels. In infants with these responses, a better outcome was reported. Hypertension was controlled in all three hypertensive infants. Adverse effects were very uncommon, and toxic effects were not observed [59].

In addition, SNP has also been successfully used in pediatric patients who needed perioperatively-controlled hypotension (orthopedic, neurosurgical, craniofacial, ear-nose-and-throat, and burn procedures). In this setting, SNP administration was not associated with an increased rate of metabolic acidosis compared with the use of anesthetic agents alone [60]. In a randomized trial from Drover et al., a 0.3 μg/kg/m SNP starting dose was used in pediatric patients requiring controlled hypotension. The infusion rate was further increased to achieve the desired blood pressure reduction. Based on their results, it was considered that an average infusion rate of 1 μg/kg/min might be appropriate. Of note, no cyanide toxicity and no measurable cyanide levels were detected in the blood samples obtained during the study [61].

8. Conclusions

SNP remains a vital component of clinical management for various cardiovascular conditions, particularly those requiring rapid hemodynamic stabilization. By recognizing its pharmacological profile and adhering to monitoring guidelines, clinicians can leverage SNP's benefits while minimizing the risks associated with its use. Ongoing research and clinical trials will continue to elucidate the optimal roles of SNP alongside current therapeutic strategies, ensuring its place in contemporary medicine. Old but Gold!

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